

# Xanax<sup>®</sup> tablets (alprazolam)

**ACTION:** XANAX (alprazolam) is a benzodiazepine with anxiolytic properties.

Orally administered alprazolam is readily absorbed in man with peak plasma concentrations occurring 1 to 2 hours following administration. The half-life range of alprazolam is 6 to 20 hours following single dose administration. With multiple doses, given 3 times daily, steady state is reached within 7 days. Alprazolam and its metabolites are excreted primarily in the urine. Degradation of alprazolam occurs mainly by oxidation yielding the primary metabolites  $\alpha$ -hydroxy-alprazolam and a benzophenone derivative. The  $\alpha$ -hydroxymetabolite is further transformed to demethylalprazolam. The  $\alpha$ -hydroxy-alprazolam and demethylalprazolam are active and appear to have half-lives similar to alprazolam but are present at only low levels in the plasma. Alprazolam is 80% protein-bound.

In sleep laboratory studies in man, alprazolam decreased sleep latency, increased duration of sleep and decreased the number of nocturnal awakenings. Alprazolam produced small decreases in both stage 3 and 4 and REM sleep. Alprazolam increased REM latency in a dose-related manner.

Alprazolam 0.5 mg, administered 3 times a day for 14 days, did not affect prothrombin times or plasma warfarin levels in male volunteers administered sodium warfarin orally.

**INDICATIONS:** XANAX (alprazolam) is indicated for the short-term symptomatic relief of excessive anxiety in patients with anxiety neurosis.

**CONTRAINDICATIONS:** XANAX (alprazolam) is contraindicated in patients with known hypersensitivity to alprazolam or other benzodiazepines. XANAX is also contraindicated in pregnancy, in infants and in patients with myasthenia gravis and acute narrow angle glaucoma.

**WARNINGS:** XANAX (alprazolam) is not recommended for use in patients whose primary diagnosis is psychosis or depression.

**Driving and Hazardous Activities:** As with other CNS-active drugs, patients receiving XANAX should be cautioned not to undertake activities requiring mental alertness, judgement and physical coordination such as driving or operating machinery, particularly in the early phases of dose adjustment, and until it has been established that they do not become drowsy or dizzy while taking XANAX. Alcohol and benzodiazepines should never be mixed when driving because of the unpredictable CNS depressant effects of this combination.

**Use in Pregnancy:** The safety of the use of XANAX in pregnancy has not been established. Therefore, XANAX is not recommended for use during pregnancy. Several studies have suggested an increased risk of congenital malformations associated with the use of the benzodiazepines chloridiazepoxide and diazepam, and meprobamate, during the first trimester of pregnancy. Since alprazolam is also a benzodiazepine derivative, its administration is rarely justified in women of childbearing potential. If the drug is prescribed to a woman of childbearing potential she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become or suspects that she is pregnant.

**Use in Nursing Mothers:** Studies in rats have indicated that XANAX and its metabolites are secreted into the milk. Therefore, nursing should not be undertaken while a patient is receiving the drug.

**Use in Children and Adolescents:** The safety and efficacy of XANAX in patients under the age of 18 years has not been established.

**PRECAUTIONS:** *Use in the Elderly:* Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to the CNS depressant activity of benzodiazepines even after low doses. Manifestations of this CNS depressant activity include ataxia, over-sedation and hypotension. Therefore, medication should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation, neurological impairment and other possible adverse reactions.

**Dependence Liability:** XANAX (alprazolam) should not be administered to individuals prone to drug abuse. Caution should be observed in all patients who are considered to have potential for psychological dependence. Withdrawal symptoms have been observed after abrupt discontinuation of benzodiazepines. These include irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting and mental impairment. Since these symptoms may be similar to those for which the patient is being treated, it may appear that he has suffered a relapse upon discontinuation. It is suggested that XANAX should be withdrawn gradually if the individual is suspected of having become dependent, or the drug perhaps has been used in prolonged high doses.

**Use in Mental and Emotional Disorders:** It should be recognized that suicidal tendencies may be present in patients with emotional disorders, particularly when depressed and that protective measures and appropriate treatment may be necessary and should be instituted without delay.

Since excitement and other paradoxical reactions can result from the use of anxiolytic-sedatives in psychotic patients, XANAX should not be used in patients suspected of having psychotic tendencies. As with other benzodiazepines, XANAX should not be used in individuals with physiological anxiety or normal stress of daily living but only in the presence of disabling manifestations of an appropriate pathological anxiety disorder.

These drugs are not effective in patients with characterological and personality disorders or those with obsessive-compulsive disorders. XANAX is not recommended for the management of depressive or psychotic disorders.

**Use in Patients with Impaired Renal or Hepatic Function:** If treatment is necessary in patients with impaired hepatic or renal function, therapy should be initiated at a very low dose and the dosage increased only to the extent that it is compatible with the degree of residual function of these organs. Such patients should be followed closely and have periodic laboratory assessments.

**Laboratory Tests:** If XANAX is administered for repeated cycles of therapy, periodic blood counts and liver function tests are advisable.

**Epileptic Patients:** Since benzodiazepines may occasionally exacerbate grand mal seizures, caution is required when XANAX is used in epileptic patients and an adjustment may be necessary in their anticonvulsive medication. Abrupt withdrawal of XANAX should be avoided.

**Drug Interactions:** Benzodiazepines may potentiate or interact with effects of other CNS-acting drugs such as alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, antihistamines, phenothiazines, butyrophenones, monoamine oxidase inhibitors, tricyclic antidepressants and anticonvulsants. Therefore, if XANAX is to be combined with other drugs acting on the CNS, careful consideration should be given to the pharmacology of the agent involved because of the possible additive or potentiating effects. Patients should also be advised against the simultaneous use of other CNS depressant drugs and should be cautioned not to take alcohol during the administration of XANAX.

**ADVERSE REACTIONS:** The most frequently reported adverse reactions with XANAX (alprazolam) were drowsiness, coordination difficulties and dizziness. Release of hostility and other paradoxical effects such as irritability, excitability and hallucinations are known to occur with the use of benzodiazepines.

Other side effects less frequently reported, listed by body systems, include the following:

**Neurologic:** Blurred vision, headache, seizures, slurred speech, difficulty in depth perception.

**Psychiatric:** Agitation, mental confusion, depression, irritability, nervousness, sleep disturbances, euphoria, lethargy, stupor.

**Gastrointestinal:** Dry mouth, nausea, non-specific gastrointestinal disturbances, vomiting.

**Musculoskeletal:** Muscle spasm, muscle weakness.

**Cardiovascular:** Hypotension, palpitations, tachycardia.

**Dermatologic:** Pruritus, rash.

**Genitourinary:** Incontinence, change in libido.

**Hematologic:** Decreased hemoglobin and hematocrit, increased and decreased WBC.

**Hepatic:** Elevations of alkaline phosphatase, bilirubin, SGOT, SGPT.

**Miscellaneous:** Increased and decreased blood sugar levels.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE:** *Symptoms:* As in the management of overdose with any drug, it should be remembered that multiple agents may have been ingested. Overdose of XANAX (alprazolam) is manifested as an extension of its pharmacologic activity. Thus, varying degrees of CNS depressant effects such as somnolence and hypnosis can occur. Other manifestations of overdose may include muscle weakness, ataxia, dysarthria and particularly in children paradoxical excitement. In more severe cases diminished reflexes, confusion and coma may ensue.

Fatalities with benzodiazepines rarely occur except when other drugs, alcohol or aggravating factors are involved.

**Treatment:** Vomiting may be induced if the patient is fully awake. Vital signs should be monitored and general supportive measures should be employed as indicated. Gastric lavage should be instituted as soon as possible. Intravenous fluids may be administered and an adequate airway should be maintained.

Experiments in animals have indicated that cardiopulmonary collapse can occur with massive intravenous doses of alprazolam. This could be reversed with positive mechanical respiration and the intravenous infusion of levaterenol.

Animal experiments with alprazolam and related compounds have suggested that hemodialysis and forced diuresis are probably of little value.

**DOSAGE AND ADMINISTRATION:** The dosage of XANAX (alprazolam) must be individualized and carefully titrated in order to avoid excessive sedation or mental and motor impairment. As with other anxiolytic-sedatives, short courses of treatment should usually be the rule for the symptomatic relief of excessive anxiety and the initial course of treatment should not last longer than one week without reassessment of the need for a limited extension. If necessary, drug dosage can be adjusted after one week of treatment. Initially, not more than one week's supply of the drug should be provided and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to short courses of therapy.

**Usual Adult Dosage:** The initial adult dosage of XANAX is 0.25 mg given 2 or 3 times daily. If required, increases may be made in 0.25 mg increments according to the severity of symptoms and patient response. It is recommended that the evening dose be increased before the daytime doses. Very severe manifestations of anxiety may require larger initial daily doses. The optimal dosage is one that permits symptomatic control of excessive anxiety without impairment of mental and motor function. Exceptionally, it may be necessary to increase dosage to a maximum of 3.0 mg daily, given in divided doses.

**Elderly and Debilitated Patients:** The initial dosage is 0.125 mg 2 or 3 times daily. If necessary, this dosage may be increased gradually depending on patient tolerance and response.

**SUPPLIED:** 0.25 mg (white) and 0.5 mg (peach) scored, ovoid-shaped tablets in bottles of 100 and 1000 tablets.

Product monograph available on request. CE 1756-28

PRODUCT OF <b>Upjohn</b>	REGISTERED TRADEMARK: XANAX 824	MADE IN <b>PMAC</b>	PAAB <b>CCFP</b>
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**SCHIZOPHRENIA IS A** group of diseases with different etiologies and courses. No single treatment will control these diseases in all patients.

Schizophrenia is the commonest form of psychosis, affecting 1% of the population at some time.<sup>1</sup> In the acute phase there are prominent positive symptoms of psychological dysfunction, including formal thought disorder (looseness of associations), hallucinations, delusions and bizarre behavior.

However, the major problems caused by schizophrenia are not these florid symptoms but the deficit symptoms—longterm residual defects which the community sees. These defects include lack of drive or motivation, lack of pleasure from the activities others enjoy, lack of empathy and lack of perseverance in working towards longterm goals. Sometimes these deficits are attributed to chronic institutionalism or the effect of medication. However, psychiatrists see these deficits in many schizophrenic patients who have never been hospitalized or treated with medications. These deficits seem to be inherent, but may be accentuated by chronic hospitalization or medications.

## Stages of Schizophrenia

A physician should match the available biological, psychological and social treatments to the patient's needs. Each patient's treatment must be modified according to the phase of his

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# The Stages of Schizophrenia And Their Management

## SUMMARY

Schizophrenia is a common and chronic disease with acute exacerbations. The chronic form of the disease results in a long-standing thought disorder and psychosocial impairment. The fluctuating nature of the disease results in a variety of presentations, for which the physician must choose the appropriate biological, psychological and social therapies. The stages of schizophrenia are described in terms of the patient's reaction to his symptoms and disabilities: anxiety, denial, ambivalence, depression and acceptance. The treatment plan must be modified according to these stages and the patient's circumstances. (Can Fam Physician 1982; 28:2046-2050).

## SOMMAIRE

La schizophrénie est une maladie courante et chronique avec exacerbations aiguës. La forme chronique de la maladie résulte en un désordre à long terme de la pensée et en une altération psycho-sociale. La nature fluctuante de la maladie produit une variété de présentations pour lesquelles le médecin doit choisir les thérapies biologiques, psychologiques et sociales appropriées. Les stades de la schizophrénie sont décrits en termes de réactions du patient à ses symptômes et à ses incapacités: l'anxiété, la négation, l'ambivalence, la dépression et l'acceptation. Le plan de traitement doit être modifié selon ces stades et l'état du patient.

illness, his reaction to it and the resulting disabilities. The stages of schizophrenia which influence treatment planning are similar to Kübler-Ross's stages of dying and grief.<sup>2</sup> These stages do not always appear in pure form or in the order listed, and they are neither necessary nor inevitable during the illness. Rather, they demonstrate why continual assessment of the patient's needs and modification of the treatment plan are essential.

### *Stage of anxiety*

In the early phase, the patient or his family may be aware of but unable to explain changes in behavior and thinking. Changes are often difficult to characterize and the patient and his family experience anxiety, fear, confusion and anger as they try to comprehend the nature and causes of the changes. Only non-specific symptoms present. These include sleeplessness, anxiety, social isolation, depersonal-

ization, eccentric or alienating behavior and ruminations about failures, philosophy or mysticism.

If a physician is consulted he may not be able to reach a definitive diagnosis. Time and intensive investigation may be required to reach a firm diagnosis. At this stage it is important for physicians to elicit all the signs and symptoms of physical or mental illness and to understand the patient and family as fully as possible. Several long interviews should be set up with the patient and family to look at external stresses and precipitating events such as drug use, family conflicts or other illnesses which may cause temporary but less ominous psychotic reactions resembling schizophrenia.

Before the clinical picture crystallizes, it may be necessary to avoid antipsychotic medication as this masks the clinical picture and may alienate the patient or family. Physicians should not take a purely analytic and

passive role but should continually enquire about the signs and symptoms of psychosis or schizophrenia. Hospitalization, psychological testing or consultation may clarify the diagnosis.

### *Stage of denial*

The patient no longer acknowledges that he has any problems. This is the stage in which the patient lives in a fantasy world and does not respond to reality, reasoning or confrontation. During this stage the florid picture of schizophrenia is apparent, with autistic thinking, formal thought disorder, hallucinations, bizarre behavior, and poor judgment. The patient blames his difficulties on family, friends, society or physicians.

The physician's first responsibility is concern for the patient's safety and ability to care for himself. This usually means that the patient should be in hospital, especially during the first

psychotic break. This may have to be against his wishes if he meets legal criteria for involuntary commitment. Unfortunately, many psychotic patients are left untreated because they do not satisfy legal criteria and refuse treatment. However, family members or close friends frequently can be encouraged to confront the patient and support the decision for voluntary admission.

During the acute psychotic episode, intensive family or individual psychotherapy is usually contraindicated because the psychotic patient is past the stage of listening to his family. In addition, the patient's accusations and blame of the family may be unrealistic, painful and disruptive to other family members and may irreparably break family ties.

If the patient agrees to have his family interviewed or if he is admitted against his will, the psychiatrist or social worker should see the family. They can provide a history of the patient's early development and personality, the precipitating events before the psychotic break, and the development of signs and symptoms. The family should be supported, not blamed for the patient's illness. They may be able to offer the patient emotional, financial and social support during the psychotic phase.

In the absence of longterm 'total re-parenting' for the patient, neuroleptics offer the best chance of breaking through this psychosis.<sup>3, 4</sup> Early intervention is imperative. If a patient has been psychotic for more than three years the likelihood of effective treatment is greatly diminished. In this phase of active psychosis, oral or intramuscular neuroleptics are indicated (see Table 1).<sup>3</sup> Of acute schizophrenic patients treated with a neuroleptic in adequate dosage, 95% will

show improvement in four to eight weeks.<sup>4</sup> All neuroleptics in equivalent doses produce approximately the same degree of antipsychotic activity.<sup>4</sup>

The most common cause of treatment failure is an inadequate dose, and the most common cause of relapse is patient non-compliance.<sup>4, 5</sup> If a patient does not respond to one or more families of neuroleptics then electroconvulsive therapy (ECT) is a reasonable, effective and safe way to control acute psychotic decompensation.

#### *Stage of ambivalence*

This phase is often prolonged. The patient has some insight into his illness and yet periodically rejects any form

of treatment. He may recognize that he tends to live in a fantasy world or hears voices that others don't and yet may disagree with the diagnosis, forget his bizarre or self destructive behavior or reject medication and ECT on principle.

The patient may take medication while he is in hospital but be rehospitalized many times because of non-compliance with medication and outpatient appointments. Paranoid ideation, social isolation, frequent moves and discomfort from side effects cause some patients to leave therapy repeatedly.<sup>5, 6</sup> This is a very frustrating time for family and physicians, who often feel hurt and may find it dif-

**"Symptoms include sleeplessness, anxiety, social isolation, depersonalization, eccentric or alienating behavior and ruminations about failures, philosophy or mysticism."**

**TABLE 1**  
**Eight of the Most Commonly Used**  
**Antipsychotic Drugs**

Drug	Equivalent Dose (mg)	Daily Dose Range (mg)
Chlorpromazine	100	50-1200
Thioridazine	100	50-800
Loxapine	15	20-250
Perphenazine	8	12-64
Trifluoperazine	5	5-40+
Thiothixene	4	5-60
Haloperidol	2	2-100
Fluphenazine (oral)	2	2-20
Depot fluphenazine	0.67	12.5-100*

\*Dose given every 1-3 weeks.

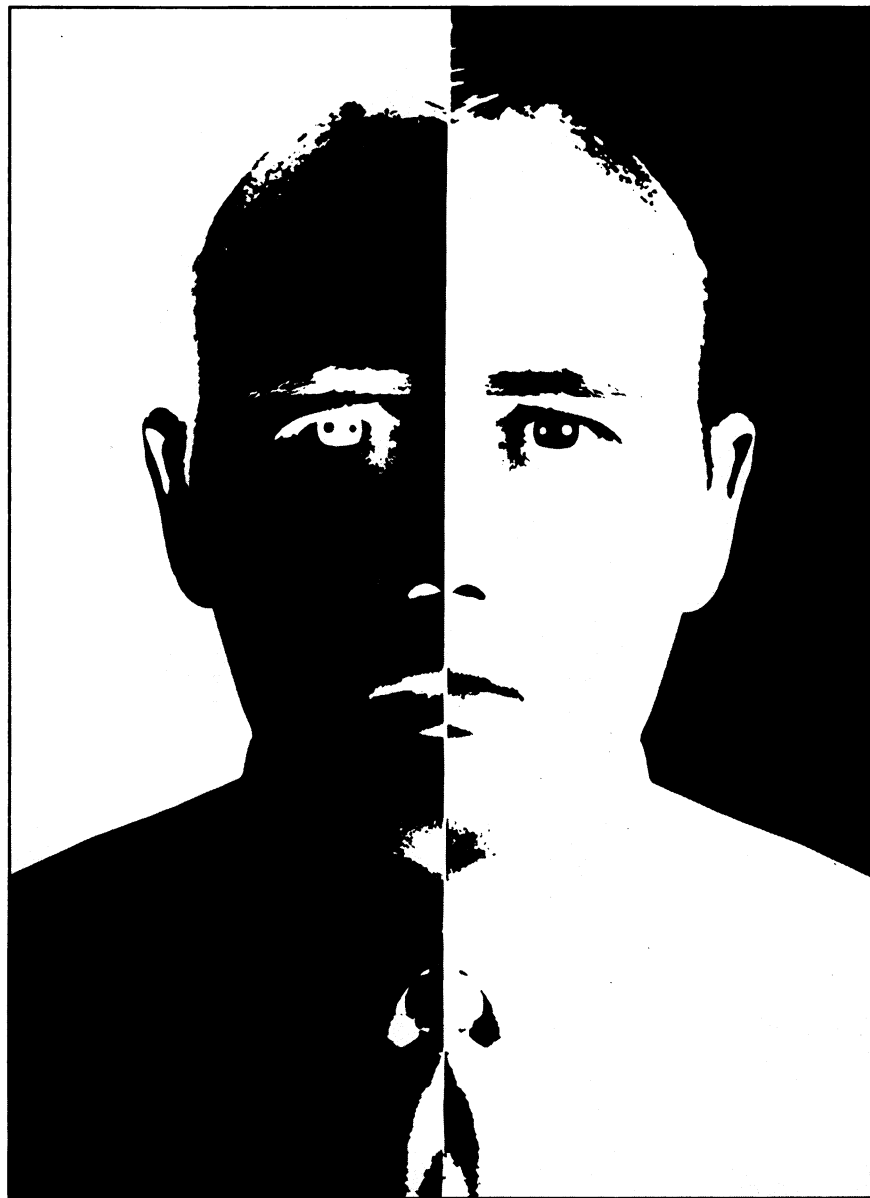


Photo courtesy of Barry E. Neubauer

difficult to accept the patient when he is more severely ill and wants care or treatment. Both family and staff have to adopt an open-door policy so the patient can return when he is in crisis.

The patient often alienates his family and they need support to ensure that their needs are met and to help disengage them from the patient's pathology. The family can profit from self-help groups and advice from others who have been through similar crises. The patient himself is often amenable to education—particularly in a group format—about the signs, symptoms and treatment of schizophrenia.<sup>5,7</sup> At this stage, rehabilitation may be helpful, although employment rehabilitation is usually unsuccessful because of the high rate of non-compliance, relapse and job failure.

The patient may be shown videotapes taken during the psychotic phase of denial, in an attempt to minimize the stage of ambivalence and non-compliance.

Long-acting injectible neuroleptics such as fluphenazine are very useful if the patient is willing to take them. They provide some protection against the patient suddenly changing his mind about his illness and treatment.<sup>6</sup>

#### Stage of depression

Schizophrenics are often thought to have no affect. Nevertheless, suicide is a frequent occurrence among them—approximately 1% every six months at one outpatient clinic.<sup>6</sup>

It is not unusual for schizophrenics to become depressed as they realize the seriousness of their illness and their inability to cope with it by themselves. They may believe their minds and lives are empty, confused and useless and see no possibility for personal or interpersonal growth. They may be afraid that the future will repeat the past.

Physicians can change the patient's beliefs in several ways. Neuroleptics can often be decreased to the lowest possible dose to make sure they do not contribute to depression.<sup>6,8</sup> Frank discussion of the diagnosis, treatment and prognosis may be very reassuring.<sup>7</sup> The patient should be seen more frequently and for longer periods, because he is now able to accept reality and, with a therapist's support, start to make some changes.

The therapist should actively provide more support and guidance than if

he were dealing with a neurotic. If depression is severe or prolonged, antidepressants or even ECT should be considered.

Sometimes the physician, patient or family will reopen the question of diagnosis at this time, but there is little doubt if documentation of the psychotic and schizophrenic symptoms in previous hospitalizations has been good.

#### Stage of acceptance

In this stage the patient accepts his history and integrates the fact of his illness into his life. Like a diabetic or an asthmatic patient, he should no longer rebel against the diagnosis or the treatment plan but accept that he cannot 'do it' by himself and that he needs drugs and/or psychotherapy.

Schizophrenics who continue taking neuroleptics have a relapse rate of 30% compared to a placebo relapse rate of 65%.<sup>4,9,10</sup> Relapses can still occur even two years after discontinuing neuroleptic medication. Educating patients and family about the early signs of schizophrenic relapse—sleeplessness, obsessive ruminations, increased fantasy life, irritability—allows the physician to prescribe the lowest possible dose of neuroleptics and reserve higher doses for the reappearance of symptoms. This maintenance level may be as low as 100-200 mg of chlorpromazine equivalents, although patients' needs vary considerably.<sup>6</sup> Some patients do not recognize the early signs of illness and higher doses keep uncomfortable symptoms under control with as few side effects as possible. Anticholinergic parkinsonian drugs are useful for short-term control of side effects when neuroleptics cannot be decreased, but in the long term they increase the risk of developing tardive dyskinesia.<sup>6,8</sup>

Garfinkel<sup>11</sup> suggests that after the first schizophrenic psychotic episode, neuroleptics should be continued for six months. After the second episode, this period is lengthened to one year. Finally, for patients who have experienced three or more psychotic episodes, indefinite maintenance of medication should be considered. The neuroleptics appear most effective in reducing agitation and controlling thought disorder, hallucinations and delusions.

Some patients with schizophrenia do not profit from longterm neuro-

leptics. These include chronic schizophrenics who have only negative symptoms.<sup>3,6,9</sup>

Rehabilitation—especially in work or education—is most effective when the patient knows his diagnosis and accepts the need for continuing biological and psychosocial treatment. Psychotherapy is usually reality-based, focusing on problem-solving and anticipating future problems. Questions about longterm goals, promotion at work, marriage and children will arise and must be discussed.

## Conclusion

One of the greatest difficulties in working with schizophrenics is setting reasonable treatment goals. It is important to recognize patients' progress or strengths as well as their limitations.

Once we understand the changing needs of patients who develop schizophrenia, we must adjust the biological, psychological and social treatments at our disposal. Meeting our patients' current and changing needs requires vigilance and judgment at every stage of illness. ●

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